REMARKS

Claims 1, 2, and 4-26 were pending. Claims 21-26 have been cancelled herein without prejudice to their presentation in another application. Claim 1 has been amended to recite that the expression is inhibited by at least 42%, support for which can be found, for example on page 84 of the specification as filed. Upon entry of the present amendment, claims 1, 2, and 4-20 will be pending.

No new matter has been added.

I. The Claimed Invention Is Not Obvious

Claims 1, 2, 4-16 and 21-26 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over the combination of Montano *et al.* (PNAS 96: 6947-6952, 1999) Milner *et al.* (Nature Biotechnology, 15:537-541, 1997, hereinafter, the "Milner reference") and McKay (U.S. Patent No. 6,133,246, hereinafter, the "McKay reference"). The Office Action alleges that it would have been *prima facie* obvious to one of ordinary skill in the art to design and utilize antisense oligonucleotides to inhibit the expression of B-cell associated protein because the Montano reference discloses the nucleotide sequence of SEQ ID NO:3 (Office Action at page 9). Applicants traverse the rejection and respectfully request reconsideration of the same in view of the following comments.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure. *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

In establishing a *prima facie* case of obviousness under 35 U.S.C. §103, it is incumbent upon the Examiner to provide a reason why one of ordinary skill in the art would have been led to modify a prior art reference or to combine reference teachings to arrive at the claimed

invention. *Ex parte Clapp*, 227 U.S.P.Q. 972 (Bd. Pat. App. Int. 1985). To this end, the requisite motivation must stem from some teaching, suggestion or inference in the prior art as a whole or from the knowledge generally available to one of ordinary skill in the art and not from appellants' disclosure, see for example, *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 U.S.P.Q.2d 1434 (Fed. Cir. 1988); and *Ex parte Nesbit*, 25 U.S.P.Q.2d 1817, 1819 (Bd. Pat. App. Int. 1992). In this respect, the following quotation from *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. App. 1993), is noteworthy:

> Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of the references." ... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force that would **impel** one skilled in the art **to do what the patent applicant has done**. (citations omitted; emphasis added)

Significantly, the Office Action identifies no "motivating force" that would "**impel**" persons of ordinary skill to modify the respective teachings of the cited references and achieve the claimed invention.

The Office Action asserts that one skilled in the art would be motivated to target and inhibit B-cell associated protein because "REA plays a role in determining the sensitivity of estrogen target cells (breast cells) to antiestrogens and estrogens, and REA plays a role in important processes including senescence, development and tumor suppression," referring to the Montano reference (Office Action, page 10). Thus, at most, this reference may provide a general motivation to further experiment. Applicants do not question the general motivation to further experiment that may be provided in the Montano reference. This general motivation, however, is not what is required to establish a case of *prima facie* obviousness. Rather, the requisite motivation that must be established is a motivating force that "would **impel** one skilled in the art to do what the patent applicant has done" (emphasis added). Indeed, there are many avenues to take when desiring to modulate the activity of a protein that may be involved in a pathway. For

example, one skilled in the art may choose to investigate the role of peptides/proteins, antibodies, or even small molecules that may inactivate the polypeptide that is encoded by SEQ ID NO:3. The Montano reference does not provide any motivation for any particular avenue of research to inhibit the function of B-cell associated protein.

Significantly, none of the cited references would have motivated persons of ordinary skill to make the substantial modifications that would have been necessary to produce the claimed invention. It is only with the improper use of hindsight and with the benefit of the Applicants' disclosure that one can discern the desirability of the particular invention now claimed.

The alleged motivation, at most, raises an inappropriate "obvious to try" standard. Indeed, the court made it clear that it is improper to reject claims as "obvious to try" where the motivation to combine references arises merely because the subject matter of the claimed invention is a promising field for experimentation, although the prior art provides only general guidance as to particular form of the claimed invention or how to achieve it. *In re O'Farrell*, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988). Without more specific suggestions in the prior art, there is insufficient motivation to combine the cited references. Furthermore, "focusing on the obviousness of substitutions and differences, instead of the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Son*, 16 U.S.P.Q.2d 1923, 1927 (Fed. Cir. 1990).

To set forth a legally sufficient *prima facie* case of obviousness, the Examiner must also show that the cited references teach or suggest a claimed invention with a reasonable expectation of success. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). No such reasonable expectation of success has been established.

The Office Action alleges that one skilled in the art would have expected to be able to find antisense compounds that inhibit the expression of B-Cell associated Protein by at least 42% because the sequence of the nucleic acids encoding B-Cell associated Protein, including B-Cell associated Protein, was known in the art, and methods of screening for antisense to a known gene was routine, and would lead to the inhibition of B-Cell associated Protein *in vitro*. That one

skilled in the art might achieve a particular level of inhibition of expression with one particular set of oligomeric compounds targeting a particular gene has no bearing on whether one skilled in the art would expect a similar level of inhibition of a different set of oligomeric compounds targeted to a different gene. In addition, the mere fact that screening assays are available and routine, however, has no bearing on whether one skilled in the art would have a reasonable expectation of success in obtaining compounds that inhibit the expression of a particular gene by a particular amount. The mere availability of an assay infers nothing as to the expected results. Indeed, it is not possible to currently predict the level of inhibition of expression achieved with any particular compound prior to carrying out the appropriate experiments.

Applicants submit herewith a Declaration of Dr. Freier, one of skill in the art of oligonucleotide technology. In paragraph 5, Dr. Freier declares that it is not possible to currently predict the level of inhibition of expression achieved with any particular oligomeric compound prior to carrying out the appropriate experiments. In paragraphs 6 and 8, Dr. Freier declares that it is not reasonable to expect for any particular gene or mRNA that oligomeric compounds having at least 42% inhibition in the expression will be obtained based upon the results obtained for a different set of oligomeric compounds targeting a different gene. Thus, simply because screening assays are available and may be routine, one skilled in the art would not have a reasonable expectation of success in obtaining compounds that will inhibit the expression of B-Cell Associated Protein by at least 42%. In addition, Dr. Freier declares in paragraph 9 that although numerous patents claiming oligomeric compounds that inhibit target expression have issued, the results reported in these patents cannot properly be extrapolated to different oligomeric compounds targeting different genes.

Therefore, even if one skilled in the art were motivated to combine the cited references in the manner indicated in the Office Action (and Applicants maintain that no such motivation has been established), one skilled in the art would not have had a reasonable expectation of success. In view of the foregoing, Applicant respectfully submits that the Office Action has failed to establish a *prima facie* case of obviousness. In particular, the Office Action has failed to provide any motivation that would **impel** one skilled in the art to modify the cited references so

as to produce Applicants' claimed inventions with a reasonable expectation of success. Accordingly, Applicants respectfully request the rejection under 35 U.S.C. §103(a) be withdrawn.

II. The Claims Are Definite

Claims 21-26 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office alleges that claims 21-26 depend on claim 1, but do not further limit claim 1. Although Applicants disagree, solely to advance prosecution, Applicants have canceled claims 21-26 without prejudice to their presentation in another application, thereby rendering the rejection moot.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

III. The Claimed Invention Is Sufficiently Enabled

Claims 15-20 and 26 are rejected under 35 U.S.C. §112, first paragraph as allegedly failing to provide an enabling disclosure. The Office Action mistakenly asserts that it would require undue experimentation for one skilled in the art to inhibit B-Cell Associated Protein expression *in vivo*. Applicants traverse the rejection and respectfully request reconsideration because one skilled in the art would be able to practice the claimed invention without being required to perform undue experimentation.

As will be recognized, the enablement requirement of §112 is satisfied so long as a disclosure contains sufficient information that persons of ordinary skill in the art having the disclosure before them would be able to make and use the invention. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (the legal standard for enablement under §112 is whether one skilled in the art would be able to practice the invention without undue experimentation). In this respect, the following statement from *In re Marzocchi*, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971), is noteworthy:

> The only relevant concern of the Patent Office under these circumstances should be over the truth of any such assertion. The first paragraph of §112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must** be taken as in compliance with the enabling requirements of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support. (emphasis added)

Any assertion by the Patent Office that an enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubts so expressed. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (C.C.P.A. 1974); *In re Bowen*, 181 U.S.P.Q. 48 (C.C.P.A. 1974). The Office Action acknowledges that the specification enables one skilled in the art to inhibit the expression of DYRK4 in cells *in vitro* using an oligonucleotide 8 to 80 nucleotides in length (Office Action, page 2). The Office Action, however, alleges that the use of antisense compounds *in vivo* is unpredictable and is not enabled by the present application.

The Office Action asserts that the present application, and also the prior art, allegedly does not support a correlation of *in vitro* results with *in vivo* results, especially when there are no working *in vivo* examples in the present application. In support of its allegations that the field of antisense is unpredictable, the Office Action refers to Branch (TIBS, 1998, 23, 45-50, hereinafter, the "Branch reference"), Crooke (Antisense Research and Application, 1998, Springer-Verlag, pp1-50, hereinafter the "Crooke reference"), Palu et al. (J. Biotechnology, 1999, 68, 1-13, hereinafter the "Palu reference"), Tamm et al. (The Lancet, 2001, 358, 489-497, hereinafter the "Tamm reference"), Agrawal et al. (Mol. Med. Today, 2000, 6, 72-81, hereinafter the "Agrawal reference"), and Chirila et al. (Biomaterials, 2002, 23, 321-342, hereinafter the "Chirila reference"). None of the cited references, however, support the position taken in the Office Action.

According to the Office Action, the Branch reference teaches that *in vivo* application of nucleic acids is "a highly unpredictable endeavor due to target accessibility and delivery issues," (Office Action, page 4). The Branch reference, however, does ***not*** teach that such barriers are insurmountable. Rather, the Branch reference concludes by stating, "there is growing evidence that antisense molecules can be useful pharmacological tools when applied carefully," (see, page 50, left column of the Branch reference), indicating that the skilled artisan sees promise in the use of antisense even though some experimentation may be needed to optimize parameters. Branch does ***not*** teach, however, that any such experimentation would be undue.

Also according to the Office Action, the Crooke reference teaches that "cell culture examples are generally not predictive of *in vivo* inhibition of target genes," (see, Office Action at page 4; referring to pages 34-36 of the Crooke reference). Applicant's undersigned representative has thoroughly examined the Crooke reference and is unable to locate any teaching that one skilled in the art would not accept Applicant's specification as an enabling disclosure. Indeed, the Crooke reference, in fact, summarizes reported activity of antisense oligonucleotides in animal models. For example, Table 1 on pages 23 to 24 lists cardiovascular models (10 targets listed in rats), inflammatory models (7 targets listed in mice and rabbits), cancer models (13 targets listed in mice and rats), neurological models (36 targets listed in rats, chickens, rabbits, and mice), and viral models (3 targets listed in mice and ducks). Thus, if anything, the entirety of the Crooke reference teaches that *in vivo* administration of antisense compounds would be expected to have at least some activity *in vivo*.

The Office Action also alleges that "the high level of unpredictability regarding the prediction of antisense efficacy in treating disease states was illustrated in the clinical trials results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease" where the placebo treatment was "found to be more successful than the antisense treatment." (Office Action, page 3). While the ISIS 2302 trial did not meet the primary endpoint for FDA approval purposes, there is no indication in the BioWorld Today article that this antisense drug fails to exert an effect in clinical subjects. Indeed, ISIS 2302 only reached the stage of Phase III clinical trial by first having demonstrated earlier Phase I safety and Phase II clinical effects in clinical subjects. More

fundamentally, the Examiner's apparent desire to see clinical data establishing efficacy for patentability of an antisense drug simply does not take into account the realities of drug development. While it might be the ultimate goal of the clinician to achieve marketing approval based upon on single Phase III pivotal clinical trial, it is a reality of the clinical trial process that predetermined end points are often not met. Failure of the first Phase III clinical trial does not necessarily mandate that marketing approval is not obtainable. Indeed many drugs ultimately get marketing approval having failed their first Phase III clinical trial. Valuable information can be gained from a failed clinical trial that can then be then used to design a more successful follow-up second clinical trial. Subsequent Phase III trials have ultimately lead to FDA marketing approval of many other drugs. Achieving a particular therapeutic endpoint in a clinical trial requires optimal dosing levels for that particular statistical endpoint. Achieving remission requires not only that the target selected for drug action be causally related to the result, but that it act without countervailing influences from other physiological targets or disease-related events. Given these variables, it is not surprising that in a complex disease, such as Crohn's disease, the vast majority of drugs do not achieve FDA "success" on the initial Phase III clinical trial. Nonetheless, such drugs are patentable. *In re Brana*, 34 USPQ.2d 1436, 1442 (Fed. Cir. 1995).

Additionally, Applicants wish to apprise the Examiner of a press release dated September 10, 2003, in which Genta Incorporated announced results from its successful Phase 3 clinical trial in which the effects of the antisense drug Genasense™ against malignant melanoma were studied (see, Exhibit A attached hereto). These results, along with the other reports of antisense publications (discussed below), establish that antisense technology does work *in vivo* in accordance with the principles and guidance set forth in the present application. Accordingly, the Genasense™ results further refute the Examiner's allegations that antisense remains a highly unpredictable art.

The Office Action asserts that the Palu reference teaches that the success of gene delivery using virally directed vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (see, Office Action at page 3).

Whether or not the Palu reference indeed teaches this, the Palu reference is irrelevant in determining whether Applicant's claimed invention is enabled. The Palu reference is directed to gene therapy, which, as defined in the Palu reference itself, is "transferring a therapeutic gene into human somatic cells in order to treat a disease" (see, Abstract). In contrast, Applicant's claimed methods do not encompass gene therapy. Indeed, Applicant's claimed methods are not directed to transferring the gene for B-Cell Associated Protein into somatic cells in order to replace a missing or defective gene so as to treat a disease. Thus, the Palu reference is entirely irrelevant in determining the enablement of Applicant's claimed methods.

The Office Action asserts that the Tamm reference concludes that proof of clinical efficacy of antisense oligonucleotides in the field of oncology is missing. The Examiner, however, has used one sentence from the Tamm reference out of context while ignoring many other teachings of the Tamm reference. Indeed, the sentence following the sentence referred to in the Office Action teaches that "large controlled trials are needed to show that antisense oligonucleotides are better than other treatment approaches." Clinical efficacy of oligonucleotides that are better than other treatment approaches is not the proper standard for enablement. Further, the Tamm reference lists in Panel 1 numerous antisense oligonucleotide targets in oncology tested *in vitro* and in animals. In addition, the Tamm reference suggests numerous other oncology targets for antisense therapy (see, pages 494-495 of the Tamm reference). The Tamm reference also teaches:

> New hope for the idea of antisense is provided by the results of a study done by Jansen and colleagues, which show that, besides the clinical benefit for patients with advanced melanoma, systemic treatment with antisense oligonucleotides results in the downregulation of the target protein within the target tissue. This study is a milestone in the field of antisense, since the results suggest that the principle of antisense works, not only with local treatment, as shown with fomivirsen, but also with systemic treatment with antisense oligonucleotides.

(see, page 495 of the Tamm reference). Thus, when the Tamm reference is examined in its entirety, one skilled in the art would not conclude that Applicant's claimed methods are not enabled.

The Agrawal reference is asserted in the Office Action to teach various factors contributing to the unpredictability of antisense therapy including 1) non-antisense effects attributed to secondary structure and charge, and 2) biological effects exerted by sequence motifs existing within the antisense sequences, and 3) cellular uptake. The Agrawal reference actually teaches that the factors listed in 1) and 2) can directly or indirectly influence the specificity and mechanism of action of antisense oligonucleotides. As a preliminary matter, Applicant's claimed methods do not require specificity or a particular mechanism of action. Taken in its entirety, the Agrawal reference supports the enablement of *in vivo* administration of antisense oligonucleotides. Regarding cellular uptake, the Agrawal reference reports that the use of cellular uptake facilitators may enhance uptake of oligonucleotides. The Agrawal reference does not teach that oligonucleotides cannot be taken up by cells *in vivo*. In addition, the Agrawal reference lists in Table 1 fifteen targets that for oligonucleotide therapy that are currently in clinical trials. Further, the Agrawal reference concludes:

> Many questions about the effects of antisense oligonucleotide sequence, secondary structures, cellular uptake, metabolism, excretion, tissue distribution, side effects and mechanism of action have been answered to a large extent, if not completely, in the past few years....it is becoming clear that antisense oligonucleotide therapeutics can in fact be as simple as complementary base recognition.

Thus, when the Agrawal reference is examined in its entirety, one skilled in the art would not conclude that Applicant's claimed methods are not enabled.

The Office Action asserts that the Chirila reference teaches that uptake of antisense oligonucleotides by target cells is a rate limiting step that has yet to be overcome in achieving predictable clinical efficacy (referring particularly to pages 326-327). In fact, the Chirila reference reports many methods and compounds that can be used to enhance cellular uptake. Further, many of the many methods and compounds that can be used to enhance cellular uptake mentioned in the Chirila reference are also taught in Applicant's specification. Indeed, Applicant's specification is replete with methods and compounds that can be used to enhance cellular uptake, if so desired. The Chirila reference in no way teaches that antisense

oligonucleotides cannot be taken up by cells. That additional methods and compounds for enhancing cellular uptake may be desired does not amount to undue experimentation.

The M.P.E.P discusses the issue of correlation of *in vitro* and *in vivo* data. The M.P.E.P is very clear that it is the overall state of the art that is important for determining the unpredictability of a field, not one or two references. Indeed, the M.P.E.P states:

> In this regard, the issue of 'correlation' is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, ***the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition.*** In *re Brana,* 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications)...***A rigorous or an invariable exact correlation is not required*** as stated in *Cross v. Iizuka,* 753 F.2d 1040, 1050, 224, USPQ 739, 747 (Fed. Cir. 1985).

(M.P.E.P 2164.02, emphasis added).

It appears that the Examiner is under the impression that an "exact correlation" is required, while the M.P.E.P clearly states that it is not. Enablement does not require 100% success. In *Wands*, the claims were found to be enabling even though only 4 out of 143 (only 2.8%) hybridomas producing monoclonal antibodies were successful. *In re Wands*, 8 U.S.P.Q.2d 1400, 1406 (Fed. Cir. 1988).

The Office Action has failed to take into account numerous references that more accurately describe the status of the field of antisense technology at or prior to the filing date of the present application (December 13, 2001). Indeed, the state of the prior art as a whole does not support the position taken in the Office Action. A recent survey of the relevant scientific literature demonstrates that there is a correlation between *in vitro* results and *in vivo* data in the field of the present invention and that *in vivo* use is not unpredictable. Thus, this survey demonstrates numerous examples of correlation between *in vitro* experiments and *in vivo* experiments. For example, in Smith et al. (Clinical Cancer Research, 2001, 7, 400-406), data are discussed demonstrating inhibition of bcl-2 expression *in vitro* and *in vivo*. In Dwyer et al.

(Clinical Cancer Research, 1999, 5, 3977-3982), the administration of an antisense compound inhibited the expression of *c-raf*-1 mRNA *in vitro* and *in vivo*. Based on these results the authors performed a clinical trial in human patients where expression of *c-raf-1* was inhibited. In Miyake et al., (Clinical Cancer Research, 2000, 6, 1655-1663) the authors provide data that demonstrates the inhibition of TRPM-2 both *in vitro* and *in vivo*. In Wang et al., (Clinical Cancer Research, 2001, 7, 3613-3624) the authors discussed *in vitro* inhibition of *mdm-2* expression followed by data demonstrating *in vivo* inhibition of *mdm-2* expression. In Berg et al., (J. Pharmacology and Experimental Therapeutics, 2001, 298, 477-484) the authors demonstrate *in vitro* and *in vivo* inhibition of thymidylate synthase expression. Tortora et al. (Clinical Cancer Research, 2001, 7, 2537-2544) discusses results where antisense oligonucleotide against protein kinase alpha type I (PKAI) inhibit expression *in vitro* and show antitumor activity *in vivo*. In Tortora, the authors combine PKAI antisense compounds with bcl-2 antisense compounds and demonstrate *in vitro* inhibition along with anti-tumor activity *in vivo* characterized by reduced tumor volume and increased survival, which was assumed to be due to the inhibition of PKAI and bcl-2. In Olson et al. (Clinical Cancer Research, 2001, 7, 3598-3605), inhibition of human angiogenin expression is described *in vitro* and *in vivo*. Applicants attach hereto copies of the above-identified references along with other references that demonstrate a correlation between *in vitro* and *in vivo* data. These articles and others available in the art demonstrate that a person of ordinary skill in the art would accept that *in vitro* inhibition of a specific gene's expression ***does*** correlate with *in vivo* inhibition.

In addition, Applicants respectfully remind the Examiner that the absence of working examples "should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement," and "the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970))." (M.P.E.P § 2164.02) Applicants further point out that a determination whether *in vivo* data are sufficient for a drug approval by the Food and Drug Administration (i.e., clinical efficacy) is not the same as a determination whether a correlation exists between *in vitro* and *in*

vivo data for patentability purposes. (See, M.P.E.P. 2164.05, "considerations made by the FDA for approving clinical trials are ***different*** from those made by the PTO in determining whether a claim is enabled.") (citations omitted, emphasis added).

Thus, when taken as a whole, the state of the art, at the time of the application's filing, including the references cited in the Office Action, does ***not*** support the allegation that the field of antisense is unpredictable and that there is no correlation between *in vitro* and *in vivo* results. Therefore, the overall state of the art in the field of antisense does not teach that antisense technology *in* vivo is unpredictable. One of ordinary skill in the art would not agree with the unsupported assertion that *in vitro* data does ***not*** correlate with *in vivo* data. Indeed, the Office Action has not provided any concrete evidence that the claimed invention is not enabled. Thus, the specification enables the pending claims of the present application.

In addition, the present application provides a ***reasonable amount*** of guidance with respect to the direction in which the experimentation should proceed. The present specification outlines the types of compounds that can be used and methods used to inhibit B-cell associated protein expression in cells and tissues. Even if a person of ordinary skill in the art may have to undertake additional experiments to use the invention, which are never particularly identified in the Office Action, the additional experimentation does not make it undue. "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." (M.P.E.P. § 2164.01). The types of experiments that the Office Action may allude to are merely routine in the art, even if they are complex.

The Office Action further alleges that Applicant's specification does not enable any and all diseases or conditions associated with B-cell associated protein. B-cell associated protein is clearly involved in "various cellular processes, including development, tumor suppression, and senescent processes, as admitted in the Office Action (see, Office Action, page 8). Further, Applicant's specification, as argued above, sufficiently enables one skilled in the art to administer compounds having 8 to 80 nucleobases targeted to a nucleic acid molecule encoding B-cell associated protein to an animal. Further, one skilled in the art would expect to achieve at least some level of inhibition of expression of B-cell associated protein. Thus, any disease or

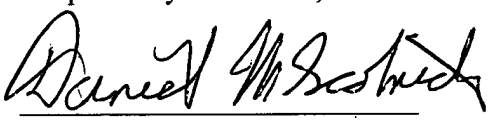
condition in which B-cell associated protein expression plays a role would be expected to be effected to at least some degree by the compounds disclosed in the present invention. Applicants respectfully remind the Examiner that claim 16 is not directed to a method of "curing" any and all diseases associated with the expression of B-Cell associated protein.

Thus, the Examiner has not established a *prima facie* case of nonenablement. One having ordinary skill in the art would be able to make and use the claimed invention using the application as a guide. Applicants cite numerous references that support enablement. Based on the evidence as a whole, the claims are enabled -- one of ordinary skill in the art would be able to make and use the claimed invention without undue experimentation using the application as a guide. The field of antisense is not unpredictable. In addition, one skilled in the art would believe that *in vitro* data correlates with *in vivo* data. No undue experimentation is required to practice the pending claims. Thus, the pending claims of the present application are enabled. Accordingly, Applicants respectfully request that the rejection of claims 15-20 and 26 under 35 U.S.C. § 112, first paragraph be withdrawn.

V. Conclusion

The claims are in condition for allowance. An early Notice of Allowance is therefore earnestly solicited. Applicants invite the Examiner to contact the undersigned representative at (215) 665-6928 to clarify any unresolved issues raised by this response.

Respectfully submitted,



Daniel M. Scolnick, Ph.D.
Reg. No. 52,201

Date: **October 5, 2004**

COZEN O'CONNOR, P.C.
1900 Market Street
Philadelphia, PA 19103-3508
Telephone: (215) 665-2000
Facsimile: (215) 701-2029

Attachments: Declaration of Dr. Freier
Cited References